Eur J Vasc Endovasc Surg **29**, 209–212 (2005)
doi:10.1016/j.ejvs.2004.09.014, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

SHORT REPORT

Heparin-induced Thrombocytopenia with Acute Aortic and Renal Thrombosis in a Patient Treated with Low-molecular-weight Heparin

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Heparin-induced thrombocytopenia is a rare but serious complication of heparin therapy. Most of cases are related to unfractionated heparin, but a few are due to low molecular weight heparin sometimes associated with unfractionated heparin.
A patient with pulmonary contusions after chest injury developed a catheter related subclavian vein thrombosis on day 16. He was treated by increasing doses of low molecular weight heparin. Aortic and renal thromboses occurred on day 21. Surgical thrombectomy, performed after starting alternative anticoagulation treatment led to complete arterial recovery.
In case of suspicion of heparin-induced thrombocytopenia, with unfractionated or low-molecular-weight heparin, heparin treatment must be discontinued before the results of biological tests become available. Arterial and/or venous thrombosis is a serious complication of heparin-induced thrombocytopenia. The treatment has two aims: first, to restore arterial patency by clot removal by thrombectomy, bypass or thrombolysis, and second, to avoid new thrombosis formation by substitutive anticoagulation treatment: danaparoid may have cross-reaction with heparin, or lepirudin has anaphylactic risks and needs biological follow-up.
Heparin-induced thrombocytopenia and thrombosis can be complicated by death or disabilities such as amputations, stroke, renal or bowel infarction.
Once HIT has been diagnosed heparin should never be given again, but if cardiopulmonary bypass is required, it might be reintroduced during operation only if serum antibodies have disappeared.

Keywords: Heparin; Thrombosis; Thrombocytopenia.

Introduction

Because subcutaneous low-molecular-weight heparin is associated with a lower risk of bleeding it is routinely recommended as a safer alternative to intravenous heparin as a prophylactic measure against venous thromboembolism. Unlike intravenous heparin, it is thought to be associated with a much lower rate of HIT.

Heparin-induced thrombocytopenia, defined as a sudden decrease in the platelet count, usually appears 5–15 days after the start of heparin therapy.[1] It may manifest as a biological observation alone, but its severity depends on the outcome of thrombotic complications involving deep veins, or arteries, or both. Since, the first case of thrombocytopenia with arterial thrombosis during heparin therapy was described in 1958,[2] the pathophysiology of this paradoxic phenomenon is now better understood, and prevention as well as substitution treatments are standardized. Although low-molecular-weight heparin was initially proposed for the treatment of heparin-induced thrombocytopenia,[3] we report an unusual case of a patient in whom low-molecular-weight heparin was the cause of thrombocytopenia. This report is instructive because it alerts the medical community and especially vascular surgeons to a rare but dramatic drug-induced complication that they

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1078–5884/000209 + 04 $35.00/0

might otherwise not suspect and may need to face more often in the future.

Case Report

A 44-year-old man, with a history of smoking, fell down the stairs and injured the lower left chest. He suffered no visceral lesions but had rib fractures and a pulmonary contusion. He was hospitalized in the intensive care unit for assisted ventilation and received anti-thrombotic prophylaxis with low-molecular-weight heparin as well as the introduction of a radial arterial line, which was flushed through daily with a heparin solution. On day 7, chest drainage was needed for hemothorax and atelectasis. On day 16, a venous peri-catheter thrombosis developed in the subclavian vein. After removal of this catheter, therapy with low-molecular-weight heparin, routinely prescribed in the intensive care unit, was increased. The platelet count was low (125×10^9/l, normal count 150–400×10^9/l). On day 21, an acute lower limb ischemia developed, and the femoral pulses almost disappeared. The duplex ultrasound investigation showed indirect signs of left iliac stenosis and of right iliac thrombosis. Over the next 7 days, the platelet count decreased to 48×10^9/l (Fig. 1). The patient was promptly transferred to our vascular surgery unit for treatment.

Examination on arrival showed that the ischemia had partially regressed, and the patient had only minor neurological signs. An abdominal computed tomographic (CT) scan with contrast injection showed a thrombus in the aortic bifurcation and proximal iliac arteries, as well as a thrombus involving the intrarenal aorta segment and the origin of the right renal artery (Fig. 2). There was no lumbar pain, and no renal failure. A serum antiplatelet factor 4 antibody test was positive. Heparin was therefore discontinued and substituted with the anticoagulant danaparoid until the platelet count improved. At surgery, performed on day 27 as ischemia was moderate, two distinctive white clots in the intrarenal aorta and right renal artery (Fig. 3) were removed by thrombectomy through a medial approach after suprarenal artery clamping, and other clots were removed from the distal aorta and proximal iliac arteries after infrarenal clamping. The operation proceeded without problems, and the peripheral pulses immediately recovered. The postoperative period was complicated by septic shock from a pulmonary infection treated medically by assisted ventilation and antibiotic therapy. A postoperative duplex ultrasound follow-up scan revealed patent aortic, iliac, lower limb and renal arteries. After the infection resolved the postoperative period was uneventful and the patient was discharged. A 6-month course of anticoagulant treatment with fluindione was prescribed. Six months after the initial event, the patient was asymptomatic and the follow-up duplex ultrasound examination yielded normal findings.

Discussion

The patient we describe received low-molecular-weight heparin for anti-thrombotic prophylaxis after a chest injury followed by an increased dose for catheter-related thrombosis. Arterial thrombosis related to low-molecular-weight heparin has been described in only a few cases.[4–9] In a report of prospective studies of surgical patients, heparin-induced thrombocytopenia developed in 2/1288 patients prescribed low-molecular-weight heparin and in 54/1597 prescribed unfractionated heparin.[10] None of the reported cases of heparin-induced thrombocytopenia were associated with clinical thrombosis. In retrospective cohort studies of heparin-induced thrombocytopenia, an associated thrombosis was noted in 7–97% of cases, and the ratio of venous to arterial thrombosis was 0.6–4.3.[10]

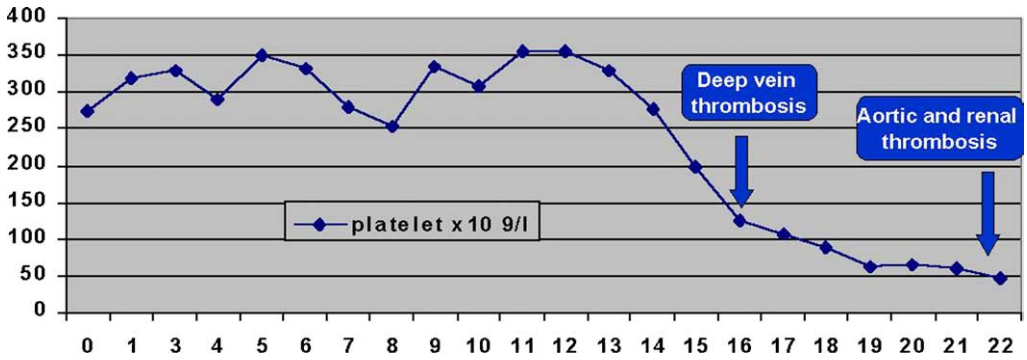

Fig. 1. Progressive changes in the platelet count.

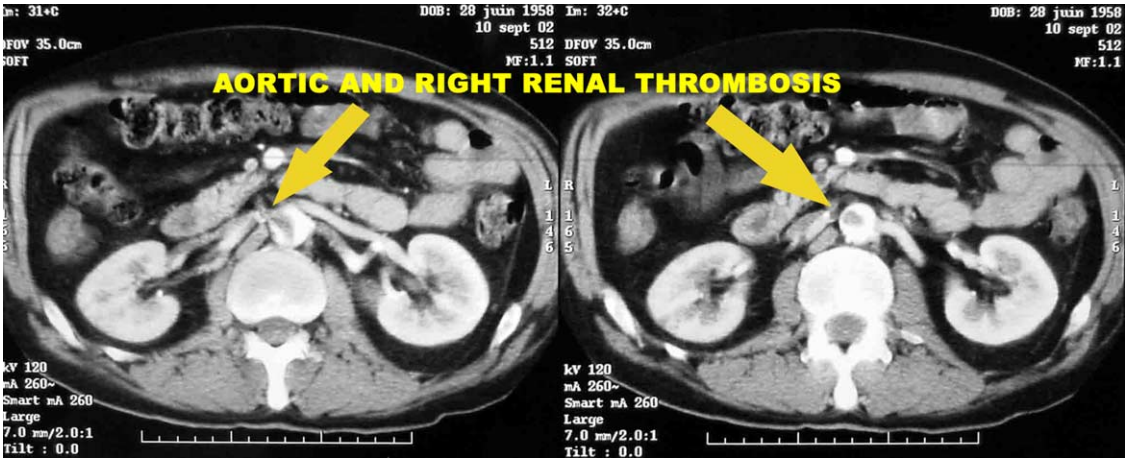

Fig. 2. CT scan showing intrarenal aortic thrombosis extending to the right renal artery.

In this case, thrombocytopenia developed 15 days after the patient received heparin. Heparin-induced thrombocytopenia typically appears from 5 to 21 days after the beginning of heparin treatment, unless heparin has been given for any reason in the preceding 100 days.[11] Heparin-induced thrombocytopenia may develop up to 40 days later after treatment with low-molecular-weight heparin than after treatment with unfractionated heparin.[12] Our patient's clinical records make no mention of serum tests for heparin-dependent IgG antibodies. The frequency of heparin-dependent IgG antibodies is reportedly higher in patients receiving unfractionated heparin than in patients receiving low-molecular-weight heparin.[11]

Fig. 3. Figure showing 'White Clot' of fibrin and platelets removed from the aorta.

As the acute aortic and renal thrombosis in our patient underlines, aortic thrombosis in heparin-induced thrombocytopenia may involve any arterial segment from the aortic arch to the bifurcation and any collateral branches.[13–15] Arterial thrombosis due to heparin-induced thrombocytopenia may be associated with deep-vein thrombosis, as in our case.[16]

In our patient the diagnosis of heparin-induced thrombocytopenia was confirmed by a positive response to antiplatelet factor 4 antibody. The currently recommended laboratory tests for biological confirmation are an immune test for antiplatelet factor 4 antibodies and a platelet activation test.

In patients who present with heparin-induced thrombocytopenia accompanied by acute arterial thrombosis, treatment has two aims: to resolve the associated arterial or venous thrombosis (surgically in our case) and at the same time prevent it from spreading. After heparin injections stop, thrombosis can be prevented with danaparoid sodium, but in 5% of the cases thrombosis worsens because of cross-reactions. Although lepirudin, proposed as a cure for thrombotic diseases, induces no cross-reactions it has an anaphylactic risk, and a risk of bleeding that necessitates regular laboratory tests to check the activated partial thromboplastin time.[16] Warfarin anticoagulation is not recommended during acute thrombocytopenia in patients with heparin-induced thrombocytopenia associated with deep-vein thrombosis because it can lead to venous limb gangrene.[11] These venous limb gangrene correlate with a high

international normalized ratio, persistent *in vivo* thrombin generation and reduced protein C activity.[18] Oral anticoagulation must be delayed until the platelet count returns to at least 100×10^9 and the risk of bleeding is controlled.

As it did in our patient, aortic thrombosis within the intrarenal aorta and extending to the iliac arteries, a rare complication known as the white clot syndrome, generally responds to surgical thrombectomy,[19] with or without bypass.[14] Some patients have been successfully treated by thrombolysis with urokinase, or streptokinase.[15] Our patient could not be treated with thrombolytic agents because of his recent thoracic injuries and treatment.

Despite the diagnostic delay, after surgery our patient not only survived but also suffered no late complications. The reported prognosis of heparin-induced thrombocytopenia in association with arterial thrombosis is poor and may reach 50% morbidity and 25% mortality.[16] Morbidity includes limb amputations, stroke with neurological disability, and bowel or renal infarction.

All patients who have had an episode of HIT must carry a warning card alerting hospital staff to their immune sensitivity to heparin. Should patients who have suffered heparin-induced thrombocytopenia with deep-vein or arterial thrombosis later need cardiac surgery with a cardiopulmonary bypass, they can receive heparin injections again provided that serum antibodies have disappeared.[17]

In conclusion, thrombocytopenia is an exceptional complication after therapy with low-molecular-weight heparin. The thrombotic lesions may nevertheless be as severe as the better known lesions caused by unfractionated heparin. To avoid disability or death, heparin should be discontinued and substituted with an alternate anticoagulant with appropriate surgical therapy or thrombolysis undertaken without delay.

Acknowledgements

We acknowledge Dr C. Cordier and Y. Ficheux (from Seclin, France) for transmitting us all elements of medical observation before transfer in our vascular surgery unit.

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Accepted 22 September 2004
Available online 14 October 2004